

**Translation**

PATENT COOPERATION TREATY

**PCT**

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 9933173-vegs	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/06188	International filing date (day/month/year) 03 July 2000 (03.07.00)	Priority date (day/month/year) 15 July 1999 (15.07.99)
International Patent Classification (IPC) or national classification and IPC C07K 7/56, 7/64, A61K 38/04, A61P 7/02		
Applicant MERCK PATENT GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet.  <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  These annexes consist of a total of _____ sheets.
3. This report contains indications relating to the following items:  I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 17 January 2001 (17.01.01)	Date of completion of this report 31 May 2001 (31.05.2001)
Name and mailing address of the IPEA/EP  Facsimile No.	Authorized officer  Telephone No.

**I. Basis of the report**

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

- ☐ the international application as originally filed.
- ☒ the description, pages 1-31, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☒ the claims, Nos. 1-9, as originally filed,  
Nos. \_\_\_\_\_, as amended under Article 19,  
Nos. \_\_\_\_\_, filed with the demand,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

**2. The amendments have resulted in the cancellation of:**

- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, Nos. \_\_\_\_\_
- ☐ the drawings, sheets/fig \_\_\_\_\_

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-2, 4-7(In Part); 8-9(In Full)

because:

- ☒ the said international application, or the said claims Nos. 8-9  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See Supplemental Sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 1-2, 4-9(In Part)

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

1. Claims 8 and 9 relate to a subject matter that in the opinion of this authority falls within the scope of PCT Rule 67.1(iv). Therefore no expert report on the industrial applicability of this subject matter will be established (PCT Article 34(4)(a)(i)).
2. The search related only to Claims 1, 2 and 4-9 (see PCT/ISA/210) and therefore Claim 3 cannot be assessed. An examination can only be performed if the subject matter has been searched (PCT Rule 66.1(e)).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Claims	3 (entirety); 1, 2, 4-9 (as much as was searched)	YES
	Claims		NO
Inventive step (IS)	Claims	3 (entirety); 1, 2, 4-9 (as much as was searched)	YES
	Claims		NO
Industrial applicability (IA)	Claims		YES
	Claims	8-9	NO

**2. Citations and explanations****1. Reference is made to the following documents:**

D1: M-L VELERO, TETRAHEDRON LETTERS, vol. 37, 1996, pp. 4229-4232.

D2: WO-A-00/37487

D3: T JACKSON, JOURNAL OF VIROLOGY, vol. 71, November 1997, pp. 8357-8361

D4: S Kraft, JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, January 1999, pp. 1979-1985, mentioned in the application.

2. The present application describes cyclical peptide derivatives as inhibitors of the  $\alpha_v\beta_6$  integrin receptor, which have the sequence cyclo-(R-X<sup>1</sup>-D-X<sup>2</sup>-X<sup>3</sup>-X<sup>4</sup>-X<sup>5</sup>-X<sup>6</sup>-R<sup>1</sup>) as the general structure, where R is arginine, D is aspartate, X<sup>1</sup>-X<sup>4</sup> are specific amino acid groups and R<sup>1</sup> is lacking one or more amino acid groups, the amino acid group or groups having a length of 500 to 2,500 pm.

2.1. Since a (complete) search is available only for the peptides of Claim 3, only those peptides and the method based on them (Claims 1, 2, 4-9) have been examined.

3.1. D1 describes a cyclization method of a linear peptide (Fig. 1). The cyclical peptides are described on page 4231, last line. The present peptides differ therefrom by the amino acid sequence.

3.2. Document D2 should not be considered the prior art within the meaning of PCT

Article 33(2) since the claimed priority date can be recognized for the relevant parts of the present application (PCT Article 33(2) and Rule 64).

- 3.3. D3 shows that the  $\alpha_v\beta_3$  integrin bonds to the RGD (=Arg-Gly-Asp) peptide sequence (see abstract). These peptides do not fall within the scope of the subject matter of the application to be examined (see point 2.1).
- 3.4. D4 describes linear peptide inhibitors of the  $\alpha_v\beta_6$  integrin receptor that have the sequence  $X_{aa}-X_{aa}-D-L-X_{aa}-X_{aa}-L-X_{aa}$  as the general structure,  $X_{aa}$  representing a random amino acid group (see Table 1). These peptides are not cyclical.
- 3.5. Thus D1, D3 and D4 are not prejudicial to the novelty of the subject matter of Claims 3 (entire) and 4-9 (partial) of the present application (PCT Article 33(2)).
4. Document D4 is the closest prior art. With respect to this prior art, the technical problem to be solved lies in making available other peptide derivatives as inhibitors of the  $\alpha_v\beta_6$  integrin.

The essential difference between the inventive peptides and those of D1 lies in the cyclization of the peptide in D4.

In the present Table 1, the applicant demonstrates increased receptor binding activity in most of the cyclical peptides with respect to a corresponding linear peptide in D4. It is therefore assumed that all of the claimed peptides in Claim 3 are inventive (PCT Article 33(3)).

5. The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of Claims 8 and 9 in their present form. Patentability may depend on the wording of the claims. The EPO, for example, does not recognize the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

Figure 1, which is cited on page 4, line 16 and on page 5, line 8 is not in the originally submitted version.